Ophthalmics for Allergic Conjunctivitis
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Approved Age Range	Indication(s)
Ophthalmic Antihistamines			
alcaftadine (Lastacaft®)[1]	Allergan	≥ 2 years	Prevention of itching of the eye due to allergic conjunctivitis
azelastine[2]	generic	≥ 3 years	Treatment of itching of the eye associated with allergic conjunctivitis
bepotastine (Bepreve®)[3]	Bausch/Valeant	≥ 2 years	Treatment of ocular itching associated with allergic conjunctivitis
cetirizine (Zerviate™)[4]	Eyevance	≥ 2 years	Treatment of ocular itching associated with allergic conjunctivitis
epinastine[5]	generic	≥ 3 years	Prevention of itching of the eye due to allergic conjunctivitis
ketotifen (OTC) (Alaway®, Zaditor®)[6,7]	generic, Bausch/Valeant, Alcon	≥ 3 years	Temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair, and dander
olopatadine 0.1% (Patanol®)[8]	generic, Alcon/Novartis	≥ 3 years	Treatment of the signs and symptoms of allergic conjunctivitis
olopatadine 0.1% (OTC) (Pataday® Twice Daily Relief)[9]	generic, Alcon	≥ 2 years	Temporary relief of itchy and red eyes due to pollen, ragweed, grass, animal hair and dander
olopatadine 0.2% (Pataday®)[10]	generic, Alcon/Novartis	≥ 2 years	Treatment of ocular itching associated with allergic conjunctivitis
olopatadine 0.2% (OTC) (Pataday® Once Daily Relief)[11]	generic, Alcon	≥ 2 years	Temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair and dander
olopatadine 0.7% (Pazeo®)[12]	Alcon/Novartis	≥ 2 years	Treatment of ocular itching associated with allergic conjunctivitis
olopatadine 0.7% (OTC) (Pataday® Once Daily Relief - Extra Strength)[13]	Alcon	≥ 2 years	Temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair and dander
Ophthalmic Mast Cell Stabilizers			
cromolyn[14]	generic	≥ 4 years	Treatment of vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis
lodoxamide (Alomide®)[15]	Alcon/Novartis	≥ 2 years	Treatment of vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis
nedocromil (Alocril®)[16]	Allergan	≥ 3 years	Treatment of itching associated with allergic conjunctivitis
Ophthalmic Anti-Inflammatory Agents			
loteprednol (Alrex®)[17]	Bausch/Valeant	≥ 18 years	Temporary relief of the signs and symptoms of seasonal allergic conjunctivitis

Ketorolac ophthalmic solution 0.5% (Acular®) is indicated for the temporary relief of ocular itching due to seasonal allergic conjunctivitis and for the treatment of post-operative inflammation in patients who

have undergone cataract extraction.[18] Its safety and efficacy have not been established in patients < 2 years of age. This product is not addressed in this therapeutic class review.

OVERVIEW

Conjunctivitis, or inflammation of the conjunctiva, may occur secondary to infectious or non-infectious stimuli.[19] Seasonal, vernal, atopic, and Giant papillary conjunctivitis (GPC) are non-infectious types of conjunctivitis; infectious types include viral and bacterial. In non-infectious types, allergens cause cross-linkage of membrane-bound IgE leading to mast cell degranulation followed by a release and cascade of allergic and inflammatory mediators, such as histamine. The estimated prevalence of allergic conjunctivitis is between 15% and 40%.[20] The condition occurs in both adults and children and is one of the most common reasons for patient self-referral.[21,22] Signs and symptoms of the disorder may cause extreme discomfort. Seasonal allergic conjunctivitis usually presents bilaterally and occurs during seasonal exposure to allergens such as ragweed. Perennial allergic conjunctivitis has a similar initial presentation; however, symptoms do not have seasonal variation. The range of symptoms varies from itching and redness to swelling, excessive lacrimation, and mucous discharge. As with allergic rhinitis, avoidance of identified allergens is a part of comprehensive therapy for allergic conjunctivitis.

The American Academy of Ophthalmology (AAO) 2018 treatment guidelines recommend an over-the-counter (OTC) antihistamine/vasoconstrictor agent or use of the more effective second-generation topical histamine H_1-receptor antagonists (e.g. alcaftadine, azelastine, bepotastine, epinastine, olopatadine) for treatment of mild allergic conjunctivitis.[23,24] The guidelines do not recommend any particular ophthalmic antihistamine over another. For persistent or frequent symptoms, an agent with mast cell stabilizer activity may be used. Combination antihistamine/mast-cell stabilizing agents can be utilized for either acute or chronic disease.[25] Short courses (1 to 2 weeks) of ophthalmic corticosteroids, at the lowest potency and frequency based on response and tolerance, may be used to treat disease flares or severe symptoms. The nonsteroidal anti-inflammatory, ketorolac (Acular), is also indicated for the treatment of allergic conjunctivitis. Use of artificial tears, cool compresses, oral antihistamines, and allergen avoidance can also be employed to control symptoms.

Vernal keratoconjunctivitis (VKC) is characterized by severe eye itching, discharge, foreign body sensation, photophobia, blepharospasm, and blurred vision that is exacerbated by environmental allergens.[26,27] It is most common in children and young adults. VKC typically occurs in hot, dry climates. Eyelid thickening, ptosis, corneal ulcerations, and infection can occur, and if left untreated and severe, VKC can lead to permanent vision loss. Evidence suggests eosinophils, fibroblasts, epithelial cells, mast cells, and TH2 lymphocytes in the conjunctiva are involved in the inflammatory response. Common therapies include topical antihistamines for mild cases with the addition of topical mast-cell stabilizers for moderate cases. High pulse dosing with quick tapering of a topical corticosteroid is usually needed to reduce inflammation. Topical cyclosporine 0.05% to 2% or tacrolimus 0.1% can be added to reduce the required dose of corticosteroid, particularly in severe cases.

PHARMACOLOGY[28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45]

Therapeutic efficacy is independent of pharmacological activity.[46]

Drug	Antihistamine	Anti-Inflammatory	Mast Cell Stabilizer
Ophthalmic Antihistamines			
alcaftadine (Lastacaft)	X		X
azelastine	X		X
bepotastine (Bepreve)	X		X
cetirizine (Zerviate)	X		
epinastine	X		X
ketotifen	X		X
olopatadine (Pataday, Pataday OTC, Patanol, Pazeo)	X		X
Ophthalmic Mast Cell Stabilizers			
cromolyn			X
lodoxamide (Alomide)			X
nedocromil (Alocril)			X
Ophthalmic Anti-Inflammatory Agents			
loteprednol (Alrex)		X	

PHARMACOKINETICS[47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64]

Drug	Systemic absorption	Preservative
Ophthalmic Antihistamines		
alcaftadine (Lastacaft)	Below level of detection	benzalkonium chloride
azelastine	Systemic absorption does occur with reported plasma concentrations of 0.02 to 0.25 ng/mL after 56 days of treatment	benzalkonium chloride
bepotastine (Bepreve)	Plasma concentrations peak at 1 to 2 hours post-instillation, with a maximum concentration of 7.3 ng/mL	benzalkonium chloride
cetirizine (Zerviate)	Mean maximum plasma concentrations of 1.7 ng/mL following a single dose and 3.1 ng/mL after twice-daily dosing for one week; mean terminal half-life of 8.6 hours following a single dose and 8.2 hours after twice-daily dosing for one week	benzalkonium chloride
epinastine	Average maximum plasma concentrations of 0.04 ± 0.014 ng/ml were reached after about 2 hours	benzalkonium chloride
ketotifen	Below level of detection	benzalkonium chloride
olopatadine (Pataday, Pataday OTC)	No data	benzalkonium chloride
olopatadine (Patanol)	Measurable levels within 2 hours of dosing ranged from 0.5 to 1.3 ng/mL in a small percentage of patients	benzalkonium chloride
olopatadine (Pazeo)	Below level of detection	benzalkonium chloride

Pharmacokinetics (continued)

Drug	Systemic absorption	Preservative
Ophthalmic Mast Cell Stabilizers		
cromolyn	Systemic absorption has been reported, but at low levels	benzalkonium chloride
lodoxamide (Alomide)	Below level of detection	benzalkonium chloride
nedocromil (Alocril)	< 4% of the total dose is systemically absorbed	benzalkonium chloride
Ophthalmic Anti-Inflammatory Agents		
loteprednol (Alrex)	Below level of detection	benzalkonium chloride

CONTRAINDICATIONS/WARNINGS[65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80]

Loteprednol (Alrex) is contraindicated in patients with most viral diseases of the cornea and conjunctiva, including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in patients with mycobacterial or fungal infections of ocular structures.

In addition, hypersensitivity to a product or its excipients is a contraindication for any product in this class.

The agents in this review should not be used to treat contact lens-related irritation. All agents contain the preservative benzalkonium chloride which may be absorbed by soft contact lenses and, therefore, should not be instilled while wearing contact lenses. Lenses may be reinserted after 10 minutes following administration.

In March 2016, the FDA warned that eye drop bottles that have loose plastic safety seals or tamper-evident rings below the bottle cap may fall onto the eye when the product is used.[81] The FDA is in the process of identifying all relevant products and will require a change in the packaging design. No further information is available at this time.

DRUG INTERACTIONS

Due to the topical route of administration of the products, clinically significant systemic drug interactions are not well identified.

ADVERSE EFFECTS[82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97]

Drug	Stinging/ Burning	Headache	Eyelid Edema	Naso-pharyngitis	Conjunctival Infection	Blurred Vision	Altered Taste
Ophthalmic Antihistamines							
alcaftadine (Lastacaft)	< 4	< 3	reported	< 3	nr	reported	nr
azelastine	30	15	nr	1–10	nr	1–10	10
bepotastine (Bepreve)	2–5	2–5	nr	2–5	nr	nr	25
cetirizine (Zerviate)	1-7	nr	nr	nr	nr	1-7	nr
epinastine	1–10	1–3	nr	1–3	nr	nr	nr
ketotifen	< 5	10–25	< 5	10–25	10–25	nr	< 5
olopatadine (Pataday, Pataday OTC)	< 5	< 5	< 5	< 5	nr	< 5	< 5
olopatadine (Patanol)	< 5	7	< 5	< 5	nr	< 5	< 5
olopatadine (Pazeo, Pataday Extra Strength [OTC])	nr (< 5 abnormal eye sensation)	nr	nr	nr	nr	< 5	< 5
Ophthalmic Mast Cell Stabilizers							
cromolyn	reported	nr	reported	nr	reported	reported	nr
lodoxamide (Alomide)	15	1.5	< 1	nr	nr	1–5	nr
nedocromil (Alocril)	10–30	40	nr	1–10	nr	nr	10–30
Ophthalmic Anti-Inflammatory Agents							
loteprednol (Alrex)	5–15	< 15	nr	< 15	5–15	5–15	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. nr = not reported.

A mild taste following instillation has been reported with bepotastine (Bepreve) in approximately 25% of subjects.

SPECIAL POPULATIONS[98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114]

Pediatrics

Most of the agents in this class are safe and effective in children as young as 3 years of age, including olopatadine 0.1% (Patanol). Cromolyn sodium is approved in patients 4 years of age and older. Alcaftadine (Lastacaft), lodoxamide (Alomide), bepotastine (Bepreve), cetirizine (Zerviate), and olopatadine (Pataday, Pazeo, Pataday Once Daily Relief, Pataday Once Daily Relief-Extra Strength, Pataday Twice Daily Relief) are approved for use in children as young as 2 years of age. Loteprednol (Alrex) is not approved in those less than 18 years old.

Pregnancy

Cromolyn is Pregnancy Category B. There are no adequate well-controlled studies in women for the use of alcaftadine (Lastacaft), bepotastine (Bepreve), cetirizine (Zerviate), lodoxamide (Alomide),

loteprednol (Alrex), nedocromil (Alocril), or olopatadine 0.1% (Patanol, Pataday Twice Daily), olopatadine 0.7% (Pataday Once Daily-Extra Strength, Pazeo) in pregnancy. Olopatadine 0.2% (Pataday, Pataday Once Daily) and the remaining products in this review are classified as Pregnancy Category C.

DOSAGES[115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131]

Drug	Dosage (in affected eye[s])	Availability
Ophthalmic Antihistamines		
alcaftadine (Lastacaft)	1 drop once daily	0.25% solution (3 mL)
azelastine	1 drop twice daily	0.05% solution (6 mL)
bepotastine (Bepreve)	1 drop twice daily	1.5% solution (5 mL, 10 mL)
cetirizine (Zerviate)	1 drop twice daily, approximately 8 hours apart	0.24% solution (0.2 mL single-use container packaged as 30 per carton)
epinastine	1 drop twice daily	0.05% solution (5 mL)
ketotifen (Alaway OTC, Zaditor OTC)	1 drop twice daily every 8 to 12 hours, no more than twice daily	0.025% solution (Zaditor OTC: 5 mL; Alaway OTC: 10 mL)
olopatadine (Pataday, Pataday Once Daily Relief)	1 drop once daily	0.2% solution (2.5 mL)
olopatadine (Patanol, Pataday Twice Daily Relief)	1 drop twice daily at an interval of 6 to 8 hours	0.1% solution (5 mL)
olopatadine (Pataday Once Daily Relief-Extra Strength, Pazeo)	1 drop once daily	0.7% solution (2.5 mL)
Ophthalmic Mast Cell Stabilizers		
cromolyn	1 to 2 drops 4 to 6 times daily	4% solution (10 mL)
lodoxamide (Alomide)	1 to 2 drops 4 times daily for up to 3 months	0.1% solution (10 mL)
nedocromil (Alocril)	1 to 2 drops twice a day	2% solution (5 mL)
Ophthalmic Anti-Inflammatory Agents		
loteprednol (Alrex)	1 drop 4 times daily (shake well)	0.2% suspension (5 mL, 10 mL)

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information submitted by manufacturers. Search strategy included the FDA-approved use of all drugs in this class and allergic conjunctivitis. Randomized, controlled, comparative trials with multiple doses for ophthalmic FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance; use data analysis techniques consistent with the study question; and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored

and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and clinical importance.

Many of the studies of the ophthalmic agents for the treatment of allergic conjunctivitis are performed as single-dose studies. The studies give very little information regarding efficacy and safety regarding chronic use of these agents. Additionally, many of the studies are done using the conjunctival allergen challenge (CAC) model in an effort to induce an allergic response and evaluate drug efficacy in a short-term model. The number of patients enrolled in the studies was generally less than 100. Several comparisons to levocabastine appear in the literature; levocabastine is no longer available in the US.

Allergic Conjunctivitis

alcaftadine (Lastacaft) versus placebo

Fifty-eight subjects with a history of allergic conjunctivitis were enrolled in a double-masked, multicenter, vehicle-controlled study.[132] Outcome measures were ocular itching and conjunctival redness. The signs and symptoms of allergic conjunctivitis were induced in the subjects by a CAC. The subjects were randomized to be given either 1 drop of alcaftadine 0.25% ophthalmic solution bilaterally or vehicle bilaterally. Alcaftadine significantly lessened conjunctival redness after both 15 minutes and 16 hours of the drug administration. With an onset of action within 3 minutes and the duration of action lasting up to 16 hours, alcaftadine was more effective than its vehicle in preventing ocular itching.

azelastine versus epinastine versus and ketotifen (Zaditor)

A study compared the short-term (5-minute) ocular comfort and drying effects of epinastine, azelastine, and ketotifen in 40 patients with allergic conjunctivitis. This was a single-center, randomized, double-blind, crossover study.[133] At the first visit, patients were randomized to receive 1 drop of epinastine in 1 eye and either azelastine or ketotifen in the other eye. Ocular comfort was assessed by patients on an 11-point scale immediately and at 0.5, 1, 2, and 5 minutes after instillation. Patients were also asked to describe how their eyes felt at 3 minutes using a standardized list of positive, neutral, and negative descriptor words. The mean comfort score indicated more comfort with epinastine compared with azelastine at 0.5, 1, 2, and 5 minutes ($p<0.001$, $p<0.001$, $p=0.001$, and $p=0.019$, respectively) and compared with ketotifen immediately after instillation ($p=0.014$). The mean ocular comfort score was significantly lower with ketotifen compared with azelastine at 0.5, 1, and 2 minutes ($p=0.001$, $p=0.023$, and $p=0.028$, respectively). A majority (85%) of patients chose positive comfort descriptors to describe epinastine versus 34% with azelastine.

bepotastine (Bepreve) versus placebo

A randomized, double-masked, placebo-controlled, multicenter CAC study compared 130 patients with allergic conjunctivitis treated with bepotastine 1% or 1.5% or placebo.[134] Both strengths of bepotastine significantly reduced CAC ocular itching at onset of action and at least for 8 hours after dosing ($p\leq0.0001$). Conjunctival hyperemia reductions for bepotastine were seen only at onset of action of CAC test ($p\leq0.0125$). Only the 1.5% bepotastine strength is FDA-approved.

bepotastine (Bepreve) versus olopatadine hydrochloride 0.2% (Pataday)

In a randomized, observer-masked, single-center, crossover study 30 patients with ocular itching associated with allergic conjunctivitis accompanied by nasal symptoms were treated with bepotastine besilate 1.5% twice daily (7:00 a.m. and 4:00 p.m.) or olopatadine hydrochloride 0.2% once daily (7:00 a.m.) for 14 days.[135] Following a 7-day washout period during which only preservative-free artificial tears were used twice daily, patients were crossed over to the alternative treatment for 14 days. According to the patient mean daily diary responses, bepotastine besilate offered significantly better relief of evening ocular itch, relief of morning and evening itchy/runny nose, and relief of morning and evening ocular allergy symptoms. At study end, 63.3% and 66.7% of patients preferred bepotastine besilate 1.5% for all-day relief of ocular itching and all-day relief of itchy/runny nose, respectively. At study end, there was no significant difference in the number of patients preferring 1 treatment over the other for comfort. Overall, 66.7% of patients stated that they would prefer to treat their allergic conjunctivitis with bepotastine besilate 1.5% over olopatadine hydrochloride 0.2%.

cetirizine (Zerviate) versus placebo

Two randomized, double-masked, vehicle-controlled, CAC studies evaluated approximately 100 patients in each study with a history of allergic conjunctivitis.[136] Patients were treated with cetirizine ophthalmic solution 0.24% or vehicle ophthalmic solution and ocular itching severity score (0 no itching to 4 incapacitating itch) was assessed. A 1-unit difference was considered to be a clinically meaningful difference in ocular itching severity. In the intention-to-treat population in both trials, 0.24% cetirizine ophthalmic solution resulted in statistically and clinically significant reductions in ocular itching compared to vehicle at 15 minutes and at 8 hours after dosing ($p<0.05$).

epinastine versus olopatadine 0.1% (Patanol, Pataday Once Twice Daily Relief)

Olopatadine 0.1% and epinastine 0.05% were compared for safety and itching and conjunctival redness prevention using the CAC model in a prospective, randomized, double-blind study.[137] Screening for response to allergen challenge (n=96) occurred prior to randomization. A total of 66 evaluable patients with allergic conjunctivitis were randomized to olopatadine in 1 eye with epinastine in the other eye, olopatadine in 1 eye with placebo in the other, or epinastine in 1 eye with placebo in the other eye. Allergen was applied to both eyes 5 minutes after treatment administration. Olopatadine was associated with significantly less itching and conjunctival redness than contralateral epinastine-treated eyes ($p=0.003$, $p<0.001$, respectively). Olopatadine-treated eyes also had less chemosis ($p<0.001$), ciliary redness ($p<0.001$), and episcleral redness ($p<0.001$) than epinastine-treated eyes in the single-dose CAC model trial.

epinastine versus olopatadine 0.2% (Pataday, Pataday Once Daily Relief)

In a 7-week, double-masked, placebo-controlled patients with ocular allergic responses were randomized into 1 of 4 treatment groups to receive 1 drop of study medication in each eye: (1) olopatadine 0.2%/placebo, (2) epinastine 0.05%/placebo, (3) olopatadine 0.2%/epinastine 0.05%, (4) placebo/placebo.[138] At separate visits, patients were allergen CAC challenged at 12 hours after drop instillation to evaluate duration of action and at 5 minutes after drop instillation to evaluate onset of action. Eyes treated with olopatadine 0.2% showed significantly lower mean ocular itching scores compared to those treated with epinastine 0.05% at 5 ($p=0.024$) and 7 min ($p=0.003$) after CAC challenge. Eyes treated with olopatadine 0.2%-treated eyes also showed significantly lower mean redness scores versus epinastine 0.05%-treated eyes at all time points post-challenge (ciliary, $p\leq0.013$;

conjunctival, p≤0.015; episcleral, p≤0.006). Olopatadine 0.2% was reported to be significantly more comfortable than epinastine 0.05% at 1 minute after instillation (p=0.003).

ketotifen (Zaditor) versus nedocromil (Alocril)

In a double-blind, single-center study of 85 patients, the CAC model was used to test 3 treatments: ketotifen 0.025%, nedocromil 2%, and placebo.[139] Patients (n=85) underwent CAC screening on 2 occasions prior to randomization. During 2 different visits 14 days apart, subjects (n=59) were randomized to 1 of the 3 treatment groups. Allergen challenges were conducted at 5 minutes post-treatment at the first visit and at 12 hours post-treatment at the second visit. Ketotifen-treated eyes exhibited significantly less ocular itching than both nedocromil-treated and placebo-treated eyes at both the 5-minute and 12-hour post-treatment challenges (p<0.05 for all). Ketotifen was tolerated as well as placebo. Ketotifen instillation was significantly more comfortable than nedocromil up to 10 minutes after instillation (p<0.05). Based on comfort and subjective efficacy, 60% of patients preferred ketotifen, 21% preferred nedocromil, and 19% preferred placebo.

ketotifen (Zaditor) versus olopatadine 0.1% (Patanol, Pataday Twice Daily Relief)

A randomized, double-masked, single-center, CAC study comparing ketotifen 0.025% and olopatadine 0.1% was conducted in 53 patients.[140] Primary efficacy endpoints were ocular itching and patient satisfaction. Itching was graded on a 5-point scale at 3, 5, and 10 minutes post-challenge. After screening, the remaining 32 patients were randomized to 2 groups. The first group instilled olopatadine 1 drop in the right eye and ketotifen 1 drop in the left eye. The second group instilled ketotifen 1 drop in the right eye and olopatadine 1 drop in the left eye. Twelve hours after instillation, subjects underwent allergen challenge. Efficacy scores for olopatadine were significantly higher than ketotifen at 3 and 5 minutes post-challenge (p<0.05). Olopatadine-treated eyes were rated significantly more comfortable than those treated with ketotifen both immediately after drug instillation and 12 hours later (p<0.05).

In a double-masked study, 66 patients with seasonal allergic conjunctivitis were randomized to treatment with ketotifen 0.025% or olopatadine 0.1% instilled twice daily.[141] Patients were assessed on days 5 and 21. Responder rate was higher on day 5 for ketotifen versus olopatadine (72% and 54% for patient assessment; 88% and 55% for investigator assessment, respectively). Responder rates on day 21 for ketotifen versus olopatadine were 91% versus 55% for patient assessment and 94% versus 42% for investigator assessment, respectively. Severity scores for hyperemia and itching were significantly lower for the ketotifen group. In both groups, the most common adverse effects were burning/stinging and headache. Patients rated both drugs similarly for comfort.

In a randomized, double-blind trial, ketotifen 0.025% and olopatadine 0.1% ophthalmic solutions were compared in patients with seasonal allergic conjunctivitis.[142] Forty-nine patients were randomized to ketotifen, olopatadine, or artificial tears administered 2 drops twice daily to both eyes for 30 days. Thirty-nine patients completed the trial. At baseline, day 15, and the end of the trial, clinical sign and symptom scores for itching, tearing, physician's assessment of eyelid swelling, redness and chemosis, conjunctival cytology specimens, and occurrence of adverse events were reported. For clinical sign and symptom scores, both active treatment groups reported significant improvement in tearing and itching at day 15 and 30 compared to baseline. The artificial tears group experienced a significant reduction in tearing at both days 15 and 30. Inflammatory markers were significantly lower in active treatment groups at both day 15 and 30 compared to artificial tears. Adverse events were not reported during the 1-month trial.

ketotifen (Zaditor) versus placebo in children

Efficacy and safety of ketotifen 0.025% were evaluated in a double-blind, multicenter, placebo-controlled trial.[143] The CAC-designed study used both single and multiple doses. Patients (n=133) were between 8 to 16 years old and exhibited a positive response to allergen challenge. Patients were given 1 drop of ketotifen in 1 eye and placebo in the other eye. CAC was administered 15 minutes and 8 hours after the dose. Patients with a positive allergen reaction in both eyes were randomized to multiple dose treatment (n=60). Patients administered ketotifen in 1 eye and placebo in the other eye twice daily for 4 weeks. CAC was performed 8 hours after the last dose. Of the 55 evaluable patients, ketotifen significantly reduced ocular itching compared to placebo after CAC ($p<0.001$). Hyperemia, chemosis, and lid swelling were also significantly reduced with ketotifen ($p=0.031$). Adverse effects were similar to placebo.

loteprednol etabonate (Alrex) versus olopatadine (Patanol)

In a single-center, double-masked CAC study, 50 subjects were randomized to receive olopatadine 0.1%, loteprednol 0.2%, or placebo.[144] One drop was instilled in each eye. Because loteprednol requires a higher dose loading period for efficacy, patients in the loteprednol group received loteprednol bilaterally 4 times daily for 14 days. Fifteen minutes after drug instillation, patients underwent allergen challenge. Subjects evaluated itching at 3, 5, and 10 minutes after challenge using a standardized 5-point scale. The investigator evaluated redness at 10, 15, and 20 minutes after challenge. Difference in inhibition of itching and redness was clinically significant ($\geq$ 1 unit difference) and statistically significant ($p<0.05$) in favor of olopatadine compared with loteprednol at all 3 time points.

olopatadine 0.1% (Patanol, Pataday Twice Daily Relief) versus azelastine

In a prospective, multicenter, double-masked, allergen challenge study, 180 patients were randomized to 1 of 3 treatment groups: olopatadine 0.1% solution in 1 eye and azelastine 0.05% solution in the other eye; olopatadine in 1 eye and placebo in the other eye; or azelastine in 1 eye and placebo in the other eye.[145] The placebo was artificial tears. Two screening phases were performed to identify appropriate allergen challenge. Five minutes after the drops were instilled, subjects (n=111) were bilaterally challenged with an allergen concentration previously determined to elicit a positive conjunctival allergic response. Subjects rated itching every 30 seconds for a total of 20 minutes. Both treatments were significantly more effective than placebo at reducing itching post-challenge. Olopatadine was significantly more effective than azelastine in reducing itching at 3.5 minutes through 20 minutes post-challenge (average mean unit difference, -0.31; $p<0.05$) in the CAC model. Single-dose administration did not result in any serious adverse events.

olopatadine 0.1% (Patanol, Pataday Twice Daily Relief) versus ketorolac (Acular)

Olopatadine 0.1% solution and ketorolac 0.5% solution were compared in a randomized, double-blind, cross-over study.[146] Patients received active treatment in 1 eye (either olopatadine or ketorolac) and placebo in the other eye. Allergen challenge was administered 27 minutes after drug instillation. Two weeks later, active drug was applied to the other eye. Olopatadine was significantly more effective than ketorolac ($p<0.001$) and placebo ($p<0.0001$) in reducing hyperemia and ocular itching at all time points (3, 10, and 20 minutes). Ketorolac was not associated with a reduction in itching. Olopatadine was also significantly more comfortable than ketorolac, as reported by subjects immediately following drug instillation ($p<0.05$).

olopatadine 0.2% (Pataday, Pataday Once Daily Relief) versus olopatadine 0.1% (Patanol, Pataday Twice Daily Relief)

In a double-blind, 24-hour study, efficacy of 2 doses of olopatadine 0.1% was compared to 1 dose of olopatadine 0.2% in prevention of ocular itching associated with allergic conjunctivitis.[147] Based on CAC, no significant difference in the mean itching scores between 2 drops of olopatadine 0.1% and 1 drop of olopatadine 0.2% was observed. Both products showed significant activity at the 24-hour time point and were statistically superior to placebo. No adverse events occurred were reported.

olopatadine 0.7% (Pazeo, Pataday Once Daily Relief-Extra Strength) versus olopatadine 0.2% (Pataday, Pataday Once Daily Relief) versus placebo

The efficacy of olopatadine 0.7% was established in 2 randomized, double-blind, placebo-controlled, conjunctival allergen challenge (CAC) clinical studies in patients with a history of allergic conjunctivitis. In the first study, patients were randomized to receive olopatadine 0.7% solution, olopatadine 0.2% solution, or a vehicle ophthalmic solution and, in the second study, patients could also be randomized to an olopatadine 0.1% solution (Patanol) in addition to the other 3 arms. Patients were evaluated with an ocular itching severity score ranging from 0 (no itch) to 4 (incapacitating itch) at several time points after CAC administration. Olopatadine 0.7% demonstrated statistically significantly improved relief of ocular itching compared to vehicle at 30 to 34 minutes, 16 hours, and 24 hours after study treatment. Olopatadine 0.7% demonstrated statistically significantly improved relief of ocular itching compared to olopatadine 0.2% at 24 hours after study treatment, but not at 30 to 34 minutes after study treatment.

olopatadine 0.2% (Pataday, Pataday Once Daily Relief) versus placebo in children

Olopatadine 0.2% was evaluated for safety in 126 children and adolescents (ages 3 to 17 years) with asymptomatic eyes in a 6-week, randomized, double-blind trial.[148] Patients were randomized to once daily olopatadine 0.2% or vehicle. Safety was assessed at 3 visits and 3 interviews. No clinically relevant treatment-related changes in visual acuity, intraocular pressure, slit-lamp assessments, fundus examinations, or cardiovascular parameters were observed. Adverse events were mild or moderate.

Vernal Keratoconjunctivitis

lodoxamide (Alomide) versus cromolyn sodium

A small randomized study compared the efficacy of lodoxamide 0.1% and cromolyn sodium 4% in 31 patients between the ages of 6 and 19 years diagnosed with VKC.[149] Dosage of each agent was 2 drops 4 times daily. Eye symptom severity scores and clinical signs were evaluated pre- and post-treatment. Conjunctival impression cytologic specimens were also obtained pre- and post-treatment to detect percentages of CD4+, CD8+, CD45RA+, and CD23+ cells. While patient symptom scores and clinical signs were significantly improved after treatment in both groups, significantly lower symptom scores and clinical signs were reported with lodoxamide compared to cromolyn sodium. The percentages of $CD4^+$ and $CD23^+$ cells in tear samples of patients in both groups A and B were significantly higher in the pretreatment stage than post-treatment stage. In the post-treatment stage, lodoxamide was associated with significantly lower $CD4^+$ and $CD23^+$ cell values compared to cromolyn sodium.

SUMMARY

Numerous comparative trials using allergic conjunctivitis agents have been conducted. The trials used 1-time administration of a single dose in the eye and evaluated effects based on a conjunctival allergen challenge (CAC) model. From the results of the trials, it is difficult to declare 1 drug superior to another. Another factor used to evaluate the drugs is ocular comfort. This evaluation was also made from 1-time single dose trials. Again, the results of the trials do not support superiority of any product in the class.

Azelastine, bepotastine (Bepreve), cetirizine (Zerviate), epinastine, ketotifen (Zaditor), nedocromil (Alocril), and olopatadine 0.1% (Patanol, Pataday Twice Daily Relief) require administration 2 or 3 times daily versus other products which require 4 times per day dosing. Alcaftadine (Lastacaft), olopatadine 0.2% (Pataday, Pataday Once Daily Relief), and olopatadine 0.7% (Pazeo, Pataday Once Daily Relief-Extra Strength) are administered once daily. In February 2020, the FDA approved a prescription to over-the-counter (OTC) switch for olopatadine 0.1% (Patanol) and olopatadine 0.2% (Pataday). As a result, the OTC versions, Pataday Twice Daily Relief and Pataday Once Daily Relief, respectively, will be replacing the prescription products.

The majority of the agents in this class are indicated for acute treatment or temporary relief of allergic ocular symptoms. The published literature gives very little information regarding efficacy and safety in chronic use of these agents. Alcaftadine (Lastacaft) and epinastine carry an indication for prevention of itching of the eye due to allergic conjunctivitis. Additionally, ketorolac (Acular), which is not included in this review, is indicated for reducing inflammation and pain after cataract extraction in addition to the temporary relief of ocular itching due to seasonal allergic conjunctivitis. Mast-cell stabilizers, cromolyn and lodoxamide (Alomide), are indicated for the treatment of vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis.

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